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Is Fecal Microbiota Transplantation a Safe and Effective Treatment for Gastrointestinal Diseases?

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Abstract

Fecal microbiota transplantation (FMT) is a method of transferring feces from an individual with a healthy microbiome to a patient whose healthy gut bacteria is deficient. While this method is not a new one, it is constantly being explored and studied to determine if it can be an effective way to treat patients with different bowel diseases. The main target of most of these studies are patients with recurrent Clostridium difficile infections. Many studies were done to determine if the method is safe, and which method is most effective, as well as who can be a good donor or recipient of the treatment.

Introduction

The large intestine is comprised of the cecum, the colon, the rectum and the anal canal. The colon is the last step in the digestive tract before the feces are expelled through the anus in a bowel movement. It is a tube-like structure containing the usual four layers; the mucosa, submucosa, muscularis and serosa. Problems can occur if the mucosa becomes inflamed or infected. Bacteria colonize the large intestine and aid in the digestion of proteins and other food particles to ready them for defecation. Bacteria also play a role in the homeostasis of the gut (Tortora, 2014).

The colon is packed with bacteria that make up the human microbiome. These are symbiotic organisms that perform different functions in the human body. Research has shown that many are important for metabolism and epithelial cell growth, doing jobs that are similar to those of the endocrine system. It seems that the microbial diversity turns out to be significantly higher in adults than children, and even more so in that of the elderly. Infants are found to have an extremely low diversity. (Blaut, et al., 2002)

The many commensal bacteria in the gut influence immune function. There are a few different ways this could be true. One of these is that the bacteria can promote the health of the epithelial lining in the intestines. This strengthens the primary barrier, so that pathogens cannot pass through the lining. In addition, some of these good bacteria can help produce and secrete an anti-inflammatory response to some inflammatory cytokines. Other mechanisms include the production of secondary bile acids, and the competition for nutrients with the pathogenic bacteria (Zeng et al., 2019).

In people with a healthy gut composition, there are a different kind of bacteria that contribute to the symbiosis of the gut. These bacteria serve as an anatomical barrier to the different pathogens that enter the intestines through various ways such as with food that is ingested. The four main phyla that are found are Firmicutes, Bacteroides, Proteobacteria and Actinobacteria. (Lopetuso et al., 2013).

In a normal bacterial gut composition, there is a symbiosis in which the bacteria work together to perform different functions. Dysbiosis occurs when there is an imbalance of the different gut bacteria, often resulting in disease such as inflammatory bowel diseases (IBD), and other gastrointestinal disorders. One common disease

is infectious colitis caused by *C. difficile*. Others include gastritis, peptic ulcer, irritable bowel syndrome (IBS) and even gastric and colon cancer. (Lopetuso et al., 2013).

Methods

Research for this paper included using databases such as the Touro College Library, PubMed and Google Scholar. These were used to find peer reviewed articles on studies related to gastrointestinal diseases and FMT as a treatment.

What is C. Difficile Infection?

As a result of taking antibiotics, many patients are left with a decrease in gut bacteria diversity, namely of the commensal Bacteroidetes and Firmicutes variety. At the same time, there tends to be a proliferation of proteobacteria which include pathogenic organisms such as *C. difficile* and shigella (Staley et al., 2016). *C. difficile*, an opportunistic organism can now cause infection because it is not outcompeted by good bacteria for nutrients and other factors that help bacteria thrive. In addition, as mentioned above, there is a reduction in the bacteria that normally prevent the proliferation of these pathogens by different mechanisms. In the majority of cases, *C. difficile* is treated with the antibiotic vancomycin or other similar drugs. Often, this course of antibiotic therapy is ineffective, resulting in recurrent *C. difficile* infections. Fecal microbiota transplantation attempts to address the problem by allowing the feces of the healthy donor to aid in replenishing the depleted gut bacteria of the patient. This leads to the patient's stool bacteria becoming very similar to that of the healthy donor (Kelly et al., 2015).

Secondary Bile Acid Production by Bacteria

There is evidence that suggests that secondary bile acid production is a crucial factor in preventing *C. difficile* infections. There appears to be a difference in the bile acid composition in the colon of patients with *C. difficile* infections in comparison to those with a healthy gut composition. A bile acid analysis study was done on fecal extracts of both donors and recipients of FMT. The results demonstrated that the pre-FMT samples contained mainly primary bile acids and bile acid salts and did not contain any secondary bile acids. In contrast, the post-FMT samples, as well as the

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donor samples contained a high abundance of secondary bile acids, indicating that the bacteria from the healthy donor had an effect on secondary bile acid production. These factors seem to indicate that it is indeed the metabolic function of these bacteria that aid in preventing *C. difficile* infections (Weingarden et al., 2014).

Primary bile acids are produced in the liver. The main ones are cholic acid and chenodeoxycholic acid. Before being secreted into bile, the bile acids are chemically attached to the amino acids taurine and glycine to form bile salts. These are then secreted into bile and then used for lipid digestion in the small intestines. While most of these are reabsorbed, about 5% of them reach the large intestine where they subsequently become deoxycholic and lithocholic acids which are secondary bile acids. As mentioned before, post FMT and donor samples contained mainly secondary bile acids and few primary bile acids. Some studies have inferred that the primary bile acid taurocholic acid (cholic acid combined with taurine), is actually a requirement for *C. difficile* growth and proliferation, and is used in growth media for this organism. It was also noted that the secondary bile acids lithocholic and ursodeoxycholic acids (from chenodeoxycholic acids), inhibit the growth of *C. difficile* (Weingarden et al., 2014).

In a study done, it became apparent that the *Clostridium scindens*, of the firmicutes phylum, is the bacteria that is likely responsible for preventing infection due to its role in secondary bile acid production (Staley et al., 2016).

The bile acid experiment was done in conjunction with the bacterial diversity survey. There was a correlation between the two studies, showing that an increase of secondary bile acids came along with an increase in Bacteroides and Firmicutes. These experiments indicate that it is likely these commensal bacteria play a metabolic role in bile acid production, inhibition of the pathogenic *C. difficile*, and overall gut health (Weingarden et al., 2014).

Who is a Good Fecal Donor?

It is not completely clear who makes a good donor for FMT. It is assumed that it would greatly depend on the donor's lifestyle and diet. Though it was noted during one study that there were good outcomes from one donor in particular, it was hard to trace exactly what made that donor so effective. In addition, many FMT trials are done with multi-donor stools for increased diversity. This would cause the researchers to be unable to isolate which donor made it most effective (Quraishi et al, 2017).

There is indication that relatives are beneficial as FMT donors because they share genetics, and are likely to have a similar microbiome to the patient. Others say that it is beneficial for a patient to receive FMT from his or her spouse

because they likely have been in contact with similar pathogens and therefore may be protected from harmful effects of introducing many new bacteria to the gut. Some think that an unrelated donor is better, because they feel that someone who is not related would be more honest in answering questions that may rule them out from donating. There is not enough conclusive evidence to determine if any of these are indeed true (Kelly et al, 2015).

In gathering the donors, there is a list of exclusion factors that can rule out those who should not donate stool. These include those who have been on antibiotics in the past 3 months, have had any history of a disease that is normally transmitted by stool, or who are known to have IBD, IBS or other gastrointestinal complications or conditions. In addition, those who have had a history of autoimmune diseases, malignant diseases, chronic pain or metabolic syndromes cannot donate feces. The reason for this is because it is assumed that people who have these conditions may have an altered microbiome which might be detrimental to introduce to a patient who is already compromised (Kelly et al, 2015). In addition, someone who has an autoimmune disease is likely being treated with immunosuppressants which suppresses the body's immune system. If this was introduced into the recipient, this could be especially harmful because there is already an infection in the patient that needs to be treated, and they must have an active immune system. Additionally, it is possible that certain DNA which causes these conditions would be present in the stool and it would be very risky to introduce to the patient (Petrov, M. E., 2011). Once they have fulfilled the above requirements, they are screened for infections within a month of donating and can then donate stool (Kelly et al, 2015).

Screening Before Donations

The specific tests done to screen a donor include those that play a role in metabolic function and the digestive system in particular. Some of these include a complete blood count, as well as a c-reactive protein test which checks for inflammation within the body. In addition, they are tested for levels of creatinine and liver enzymes. The stool itself is screened for ova and parasites and *C. difficile* in particular, among other intestinal pathogens (Satokari et al, 2015).

Methods of Preparing Feces for Transplantation

The transferring of feces can be done by different procedures. Those include transplantation with an oral capsule, colonoscopy or by enema. (Kao et al, 2017). There is also debate about whether it makes a difference if the feces

were previously frozen, or if fresh stool is used. Results of trials show that there is little difference in effectiveness between these methods. Therefore, it is suggested that frozen samples be used simply because they are easier to produce and obtain (Satokari et al, 2015).

In addition to what was mentioned above, using frozen stool allows for universal donors. That means that when a potential donor is screened and found to be a good candidate, his feces can be used for multiple patients. This would also allow clinics to store the frozen feces and use them as needed (Satokari et al, 2015).

Fresh Stool for FMT

When using fresh stool for FMT, the stool must be used within a 6-hour window of time, from defecation to transplantation. With this method, approximately 30 grams of stool is mixed with 150 ml of tap water and then administered to the patient within 15 minutes of preparation. This method is very limiting, and not as readily available as frozen stool (Satokari et al, 2015).

Preparing Fecal Slurry for Colonoscopy with Frozen Stool

There are slight variations in methods of preparing frozen stool for FMT. The following is one of them:

Fresh stool is collected and stored in units of 80-100 g. To each collection, 200 ml of .9% saline is added. The resulting mixture is filtered through a stomacher bag, designed to keep samples uncontaminated, yielding 180 ml of fecal slurry. Mixing the slurry with 20 ml of 100% glycerol allows it to be frozen at -70 degrees Celsius for 2 months, until needed. For use, the slurry is defrosted overnight at 4 degrees Celsius and then reconstituted with 160 ml of .9% saline. (Kao et al, 2017)

In using fresh or frozen stool, one method of administering it is through a biopsy channel, a piece of flexible tubing in the cecum (Satokari et al, 2015).

Preparing Feces for Capsule Manufacturing

Forty ml of 100% glycerol is added to 200 ml of prepared fecal slurry and centrifuged for 20 minutes at room temperature and 400 G (gravitational force). After decanting the supernatant, the sample is then centrifuged at 4-8 degrees Celsius and 10,000 G by high speed centrifuge. The remainder of the sample is mixed to yield about 12 ml of sample containing 10^{13} microbes by estimation. This is then pipetted into size No. 1 gelatin capsules which are then encapsulated twice by size 0 and then 00, yielding 40 capsules. These capsules are then flash frozen at -55 degrees Celsius on dry ice to preserve them. Just like the fecal slurry, the capsules can remain stored at -70 degrees

Celsius for 2 months. To administer FMT, the patient swallows approximately 40 capsules within a short period of time (Kao et al, 2017).

Synthetic FMT

Vos W.M writes that synthetic FMT is likely a good alternative to the common use of donor stool. Synthetic FMT is a lab produced combination of the needed strains of bacteria, without the actual stool of the donor. The reason for this is because by the time the donor stool reaches the patient, many of the organisms are no longer viable. In addition, stool contains other wastes, mucus and pathogens. Vos suggests that administering synthetic microbiota which was cultured to get the right composition of bacteria is not only more effective, but less likely to have adverse effects as well. Synthetic FMT would not contain all the parts of the stool that are unnecessary as well as detrimental to the patient. In addition, it would allow for greater viability and microbial diversity as well as being able to be manufactured and reproduced (Vos, 2013).

Effectiveness in Treating *C. difficile* Infections

In order to determine effectiveness, a DNA sequencing test is performed to determine which bacteria were colonized in the gut of the patient post FMT treatment. In studies that were done, the patients who were treated with heterologous stool samples- that of a donor showed a greater diversity in stool microbiology than those who were treated with autologous samples- their own, i.e. the placebo group. In the heterologous stool samples, there was a significantly higher presence of Bacteroidetes and firmicutes, indicating that these are the phyla that should be present in healthy stool. In contrast, those who were treated by placebo did not contain an abundance of these bacteria. Instead, they presented with more of the *Clostridium* XIVa clade and *Holdemania* bacteria that were thought to take part in causing the *C. difficile* infection. Results from this study seem to imply that a complete engraftment- proliferation of all the bacteria, is not necessary so long as the needed bacteria are present. (Staley, et al, 2016)

In a systematic review by Cammarota, Lanio, and Gasbarrini, A. indicates an 87% success rate when comparing the data of numerous studies. The rates of diarrhea resolution varied depending on the site of the fecal transplantation. The data indicated a rate of 81% in the stomach, 86% in the duodenum-jejunum, 93% in the cecum-ascenting colon, and 84% in the distal colon. (Cammarota, et al, 2014)

A randomized trial was performed on 46 patients with 3 recurring episodes of *C. difficile*. All of these patients

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were treated with vancomycin without success. During the study, all the patients were treated by colonoscopy. Some of the patients were treated with donor stool, while others were treated with their own autologous stool. Those treated with autologous stool were checked to determine if the donor stool was indeed more effective, or similar to the placebo effect. Of the 22 who were treated with donor stool, 20 had a full recovery from *C. difficile*, accounting for a 90.9% recovery rate. In contrast, of the 24 who were treated with their own stool, only 15 recovered, which is a 62.5% recovery rate. The patients who contracted another *C. difficile* infection following FMT with autologous stool were subsequently treated with donor stool, with success. The outcome of this study seems to indicate that FMT is a safe, effective way to treat recurrent *C. difficile* infections (Kelley et al, 2016)

A study was done to determine whether transplantation by colonoscopy or by oral capsule was more efficient. The outcome of the study seems to indicate that neither one is preferable and both were effective. The factors to consider were those that an oral capsule is both less invasive and cheaper to administer. (Kao et al, 2017)

FMT for Ulcerative Colitis

Ulcerative colitis is a condition in which the mucosal layer of the colon is inflamed. Patients with this condition present with bloody stool, anemia and abdominal pain (Costello et al, 2019). A trial was done in 3 hospitals, treating 85 patients to see if FMT could work to cure ulcerative colitis in addition to the known effects of treating *C. difficile* infections. In this trial, patients were treated with stool from multiple donors to increase the biodiversity. There was also a placebo group. In both groups color and odor was added so that the patients would not know if they were receiving the real transplant. The original infusion was administered by colonoscopy, directly into the terminal ileum and caecum. The patients were monitored periodically for 8 weeks (Paramsothy et al., 2017).

Though there was not a significant majority, 27% of people who received donor FMT saw a relief of symptoms, while only 8% of placebo patients saw these effects. After the 8 weeks however, the numbers on both sides increased. It was observed that a particular bacterium of the *Fusobacterium* variety was present in those who did not have a remission of symptoms after FMT. It is important to note that majority of the patients in the placebo group had milder symptoms to begin with. The outcome of the study indicated that FMT may be a good alternative to usual steroidal therapies used for ulcerative colitis, though more research would need to be done to determine if that is indeed the case (Paramsothy et al., 2017).

A study was done to determine if anaerobically prepared stool would be as effective as aerobically prepared FMT for ulcerative colitis. The purpose of the trial was to determine if the organisms in the stool would be more viable if they were prepared anaerobically. This study was done after the study mentioned above by Paramsothy. Based on data that was collected from the above study, researchers were hopeful that FMT could be very effective in ulcerative colitis patients. This study was a variation of the first one. The outcome of the study indicated that 32% of those who received donor FMT saw an initial relief of symptoms. Nine percent of those who received autologous stool saw an initial relief of symptoms as well. (Costello et al, 2019). This data seems to be very similar to that of the aerobically prepared FMT. More trials would be needed to determine if anaerobically prepared stool is actually more effective. This study adds to the research that FMT is helpful in some cases for ulcerative colitis.

FMT for IBD

IBD is a general term for different inflammatory bowel diseases. Included in these are ulcerative colitis and Crohn's disease. As mentioned above, these diseases cause chronic inflammation of the bowel. Either of these conditions can cause colorectal cancer, and other medical problems in the individual. There is evidence that suggests that it is the microbiome gut composition that plays a role in these diseases. After seeing great success in treating recurrent *C. difficile* with FMT, researchers are hopeful that it can work as a therapeutic treatment for other conditions as well (Quraishi et al., 2017).

According to studies, it seems that IBD can be an abnormal reaction to having microbiota in the gut. Patients with this condition possess genes that view these enteric bacteria as pathogens, even those that are considered symbiotic in a healthy person. Evidence to support this study included testing on germ-free animal models that were predisposed to IBD. In addition, there were studies done in which the fecal stream was diverted. In both of these studies, it appeared that not having any bacteria present in the gut led to having no inflammatory symptoms. The activation of innate and adaptive immunity by bacteria that is normally nonpathogenic can lead to an inflammation in the gut in the absence of pathogenic bacteria (Quraishi et al., 2017).

It is noted by Quraishi et al., that though it seems that any presence of bacteria induces IBD in those that are predisposed, there are studies done that suggest that there is indeed a difference in microbial diversity in those with IBD in comparison to those with a healthy gut (Quraishi et al, 2017.) The composition is characterized by an increase

in bacteria which include Enterobacteriaceae, Pasteurella, Veillonella, and Fusobacteria, and also contains less Firmicutes, Bacteroidetes, and Clostridia (Gevers et al., 2014). It is also noted that there is an increase of Proteobacteria in those with IBD. Using FMT with IBD has been met with very limited success in the past. There has been more evidence of success with ulcerative colitis patients, than in those with Crohn's disease (Quraishi et al, 2017).

FMT for Hepatic Myelopathy

Hepatic myelopathy is a neurological complication that comes from severe liver disease. Usually, it can only be treated by a liver transplant. There was a case study done, however, that indicated that FMT may indeed be a solution to this illness. The study was done on one 45-year-old woman in China. She was admitted to the hospital numerous times, and underwent various procedures. The reasons for these included different complications such as splenomegaly, vomiting blood and other internal bleeding. The last visit was due to a weakness and stiffening in her legs. Interestingly, after being treated with 3 courses of FMT, she reported a relief of symptoms. There is no conclusive evidence that this can work in all cases. However, due to the known correlation between gut symbiosis and neurological health, the researchers say that FMT may be a good therapeutic alternative to a liver transplant as it is more available and less invasive (Sun et al, 2019).

Adverse Effects of FMT

In a randomized trial done, it was noted that there were no serious adverse effects following fecal microbiota transplantation. The study did not include anyone who was immunocompromised, or above age 75. Following FMT the patients were monitored periodically for 6 months, and none exhibited any serious symptoms in relation to FMT (Kelley et al, 2016).

Kao et al reports that two patients died following FMT, though it was not likely due to the procedure. Both had significant cardio-pulmonary disorders and both were elderly (Kao et al, 2017).

While FMT has seems to have many beneficial uses, as with any therapy, there are downsides as well. Dr. Schwartz, Gluck and Koon say that a reason for this may be because though fecal donors go through extensive screening, it is possible that they were carrying diseases that they were unaware of. They could have been asymptomatic and not have been tested for that specific pathogen. There were two cases noted of norovirus in Virginia Mason Medical Center in Seattle. Norovirus is a common contagious virus that causes gastroenteritis in many people. In those cases, the donors were asymptomatic and it

was unknown whether the virus was transmitted through the feces as there was a window of time between the collection of the feces and the actual transplantation. The most significant effect of these cases was that both patients presented with a relapse of *C. difficile* infections. It was speculated that it is possible that the norovirus altered the bacterial community present in healthy stool resulting in an ineffective FMT (Brandt, L. J., 2013).

In an FMT trial on ulcerative colitis patients, a significant amount reported adverse effects. Approximately 78% of the donor stool recipients and 83% of the placebo recipients reported gastrointestinal upset. The complaints were self-limiting, resolving on their own and having no long-term effects. In addition, 2 patients who received donor stool, and 1 who received autologous stool as a placebo presented with serious adverse effects (Paramsothy et al, 2017). The study did not mention what they were.

Quraishi et al. note that FMT should not be administered to those who have Crohn's disease with deep patch ulceration in the gut. The reason for this is because it is likely that the bacteria may translocate. That is, the bacteria may cross the organ barrier and enter into the bloodstream where it does not belong. Administering FMT in those patients could cause many harmful effects. It is different however for ulcerative colitis because in that condition the inflammation is contained to the epithelium and risk of bacterial translocation is not high (Quraishi et al., 2017).

In a letter written to the editor of The American Journal of Gastroenterology, Dr. Brandt presents his observations that there are effects of *C. difficile* that are not yet known. He noted however that it is reasonable to assume that down the line there would be adverse effects. Those may include short term affects like allergic reactions or transmitted infections. He speculates that it is likely that FMT patients may suffer long term effects such as conditions that result from an altering the recipient's microbiome to be similar to that of the donor (Brandt, L. J., 2013). It is interesting to note, however, that this was written in 2013, and articles written in later years did not report these predictions.

Why Not Oral Probiotics?

People think that probiotics are helpful for the gut microbiome. The reason for this assumption is that if some bacteria are considered good, an increase in those bacteria should be considered helpful to a person's overall wellbeing. Research has shown, however, that this may not necessarily be the case. It was noticed that certain cancer patients were not responding to immunotherapy and that majority of those patients were taking probiotic

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supplements. There is evidence that taking a probiotic supplement reduces the biodiversity in the gut. Though it does cause an increase in certain essential bacteria, those bacteria in large quantities may be harmful to other systems. For example, an increase in *Bacteroides* is said to increase metabolism, but seems to be detrimental to the immune system (Hardy, L., 2019).

There is also research that indicates that taking probiotics after a course of antibiotics actually slowed the body's response in replenishing the gut. In this study, three groups of patients were given antibiotics. One group was not subsequently treated, another was given probiotics, and the third was given autologous FMT with stool collected before they were given antibiotics. Evidence from this study indicated that those who were given probiotic supplements took significantly longer to recover than the others. This study also seems to show that FMT is indeed a good way to replenish the gut bacteria after treatment with antibiotics (Hardy, L., 2019).

Conclusion

In conclusion, there is hope that FMT can effectively treat dysbiosis of the gut. This is especially true for the case of a recurrent *Clostridium difficile* infection, where the majority of cases were cured with few or no adverse effects noted. There are studies that imply that other gastrointestinal diseases could be treated effectively as well. It was also noted that there is little difference in outcome of treatment when different methods of transplantation are used. Other than for recurrent *C. difficile* infections for which FMT has been deemed effective, more research should be done to determine if it is effective for the other mentioned diseases. Overall, FMT is a promising and innovative therapy for gastrointestinal problems.

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